Request for permission for oral testimony at Idaho Medicaid's P&T Committee meeting on 04-15-2011

Submission # 11

The following request has been:

- ○ Approved
- ☒ Denied

Gennrich, Jane - Medicaid

From: Eide, Tamara J. - Medicaid
Sent: Tuesday, March 15, 2011 4:27 PM
To: Gennrich, Jane - Medicaid
Subject: FW: Committee
Attachments: FSD00933 Toviaz 2011 Updated Medicaid Supplement.pdf; GNU00347E_RVPTH Handout_FINAL_120610.pdf

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From: Heineman, Susan M [mailto:susan.m.heineman@pfizer.com]
Sent: Tuesday, March 15, 2011 4:20 PM
To: Eide, Tamara J. - Medicaid
Subject: Committee

Hi Tami,

I would like to request time to testify for fesoterodine and growth hormones at the April 15th P&T Committee meeting. Thank you!

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Updated Data Supplement for TOVIAZ ® (fesoterodine fumarate)

I would like to present published data on TOVIAZ® (fesoterodine fumarate), including the 2 largest head-to-head superiority trials of overactive bladder (OAB) drugs. These trials were specifically designed as superiority studies to compare TOVIAZ 8 mg to DETROL® LA (tolterodine tartrate extended release capsules) 4mg.[1,2] These 2 similarly designed studies were 12-week, randomized, double-blind, placebo-controlled, multicenter head-to-head superiority trials. Consistent with the label, all subjects randomized to TOVIAZ started on 4 mg for one week, followed by TOVIAZ 8 mg for 11 weeks. All subjects randomized to DETROL LA received 4 mg for 12 weeks.

Results from the first superiority trial have previously been presented. I would like to present the results from the recently published second superiority trial. As in the first trial, TOVIAZ 8mg was superior to DETROL LA 4mg for the primary endpoint of change in mean* number of urgency urinary incontinence (UUI) episodes per 24 hours at 12 weeks relative to baseline.

Among the secondary diary endpoints, TOVIAZ 8mg showed significantly greater efficacy than DETROL LA 4mg in reducing urgency and frequency episodes per 24 hours at Week 12. The difference between TOVIAZ 8mg and DETROL LA 4mg on MVV per micturition did not reach statistical significance in this study. In pre-specified analyses, the diary dry rate (on a 3-day diary) at week 12, and improvements in patient reported outcomes (including the PPBC, UPS and OAB-q) were significantly greater among subjects receiving TOVIAZ 8mg compared with those receiving DETROL LA 4 mg.

The TOVIAZ and DETROL LA treatment groups had treatment-emergent adverse events (TEAEs) (≥2%) which included: dry mouth (27.6% for TOVIAZ 8mg; 13.4% for DETROL LA 4mg; 5.4% for Placebo), constipation (4.4% for TOVIAZ 8mg; 3.1% for DETROL LA 4mg; 1.5% for Placebo), and headache (2.8% for TOVIAZ 8mg, and 2.1% for DETROL LA 4mg; 1.3% for Placebo) which were generally consistent with those reported in previous studies and reported in the USPIs for TOVIAZ and DETROL LA.

In a 12-week, double-blind, placebo-controlled, flexible-dose study, subjects were randomized to receive either TOVIAZ 4 mg or placebo for 2 weeks.[3] At Week 2, the dose could be increased to TOVIAZ 8 mg (or a sham dose escalation for placebo) based on subjective assessment of efficacy and tolerability by the physician and their patient. 63% of subjects on TOVIAZ chose to escalate the dose compared with 73% on placebo. At Week 12, TOVIAZ was significantly better than placebo in decreasing the mean number of micturitions (the primary endpoint), UUI episodes, and urgency episodes over 24 hours.

A post hoc analysis of data from this trial evaluated efficacy and tolerability based on whether the subjects stayed on TOVIAZ 4 mg ("nonescalator") or chose the higher TOVIAZ 8 mg dose ("escalator") at week 2.[4]

For each of the OAB diary endpoints: UUI, micturition frequency and urgency and the adverse event dry mouth, the response pattern is consistent –the nonescalators have more symptom reduction and higher dry mouth at week 2 than those who chose to escalate.

Indication

TOVIAZ and DETROL LA are muscarinic antagonists indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Important Safety Information

TOVIAZ and DETROL LA are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients with known hypersensitivity to either drug or their ingredients.

Angioedema of the face, lips, tongue, and/or larynx has been reported with TOVIAZ, in some cases after the first dose. Patients should be advised to promptly discontinue TOVIAZ therapy and seek immediate medical attention if they experience edema of the tongue, laryngopharynx, or difficult breathing.

Please see additional Important Safety Information on next page, and accompanying full prescribing and patient information.

While the 63% of TOVIAZ subjects who chose to escalate had less symptom reduction on all of the endpoints at Week 2 (on 4mg dose), they experienced a greater degree of improvement over the following 10 weeks of the trial and had more dry mouth with the increased dose. At the end of Week 12, the degree of efficacy was very similar between the nonescalator and escalator groups , as was the prevalence of dry mouth.

These data suggest that some patients will require a higher dose of medication to get the same degree of efficacy as those that do not desire to increase their dose.

In summary, TOVIAZ is an effective treatment for OAB symptoms with a demonstrated tolerability profile and is available in 2 doses (4 mg and 8 mg), allowing dose adjustment based on individual patient response. TOVIAZ is the only antimuscarinic agent for the treatment of OAB symptoms that comes with the *YourWay*™ plan, a support program designed to help patients take an active role in OAB treatment.

*A Winsorized mean was utilized to account for the non-normal distribution of the data

Important Safety Information (Continued)

TOVIAZ tablets should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, controlled narrow-angle glaucoma, or myasthenia gravis. TOVIAZ is not recommended for use in patients with severe hepatic impairment.

DETROL LA capsules should be used with caution in patients with clinically significant bladder outflow obstruction, gastrointestinal obstructive disorders, controlled narrow-angle glaucoma, myasthenia gravis, and significantly reduced hepatic or renal function.

The recommended starting dose of TOVIAZ is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. Doses greater than 4 mg are not recommended in patients with severe renal insufficiency or in patients taking a potent CYP3A4 inhibitor; in patients taking a weak or moderate CYP3A4 inhibitor, careful assessment at 4 mg is advised prior to increasing to 8 mg.

The most frequently reported adverse events (≥4%) for TOVIAZ in the prescribing information were: dry mouth (placebo, 7%; TOVIAZ 4 mg, 19%; TOVIAZ 8 mg, 35%) and constipation (placebo, 2%; TOVIAZ 4 mg, 4%; TOVIAZ 8 mg, 6%).

The most frequently reported adverse events (≥4%) for DETROL LA in the prescribing information were: dry mouth (placebo, 8%; DETROL LA, 23%), headache (placebo, 4%; DETROL LA, 6%), constipation (placebo, 4%; DETROL LA, 6%), and abdominal pain (placebo, 2%; DETROL LA, 4%).

Please see accompanying full prescribing and patient information.

References:

1. Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU International 2010;105:58-66.
2. Kaplan SA et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: A prospective, head-to-head, placebo-controlled trial. *BJU Int*. Epub 2010 Sep 21.
3. Dmochowski RR et al. Randomized, double-blind, placebo-controlled study of flexible-dose fesoterodine in subjects with overactive bladder. *Urology*. 2010;75:62-68.
4. Staskin D et al. Effects of flexible dose escalation in a placebo-controlled clinical trial of fesoterodine. *Neurourol Urodyn*. 2010; 29:303-304.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Toviaz safely and effectively. See full prescribing information for Toviaz.

Toviaz® (fesoterodine fumarate)
For oral administration
Initial U.S. Approval: October 31, 2008

----------RECENT MAJOR CHANGES----------

Contraindications: hypersensitivity to tolterodine tartrate (4)	02/2011
Warnings and Precautions: Angioedema (5.1)	02/2011

----------INDICATIONS AND USAGE----------

Toviaz is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended starting dose of Toviaz is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. (2)

The daily dose of Toviaz should not exceed 4 mg in the following populations:

- Patients with severe renal impairment (CL_{CR} <30 mL/min) (2)
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. (2)

Toviaz is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). (2)

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Toviaz 4 mg extended-release tablets are light blue, oval, biconvex, film-coated, and engraved with "FS" on one side. (3)

Toviaz 8 mg extended-release tablets are blue, oval, biconvex, film-coated, and engraved with "FT" on one side. (3)

----------CONTRAINDICATIONS----------

Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients or to tolterodine tartrate tablets or tolterodine tartrate extended release capsules.. (4)

----------WARNINGS AND PRECAUTIONS----------

- Angioedema of the face, lips, tongue, and/or larynx has been reported with fesoterodine (5.1).
- Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention. (5.2)
- Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation. (5.3)
- Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks (5.4)
- Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin).In patients taking weak or moderate CYP3A4 inhibitors (e.g., erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised prior to increasing the daily dose to 8 mg. (5.7)
- Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction. (5.8)

----------ADVERSE REACTIONS----------

The most frequently reported adverse events (≥4%) for Toviaz were: dry mouth (placebo, 7%; Toviaz 4 mg, 19%; Toviaz 8 mg, 35%) and constipation (placebo, 2%; Toviaz 4 mg, 4%; Toviaz 8 mg, 6%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors. The effects of weak or moderate CYP3A4 inhibitors were not examined. (7.2)
- No dosing adjustments are recommended in the presence of CYP3A4 inducers or CYP2D6 inhibitors. (7.3, 7.4)
- There were no changes in the plasma concentrations of combined oral contraceptives containing ethinyl estradiol and levonorgestrel. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy and Nursing Mothers:* Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. (8.1) Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate. (8.3)
- *Pediatric Use:* The safety and effectiveness of Toviaz in pediatric patients have not been established. (8.4)
- *Geriatric Use:* No dose adjustment is recommended for the elderly. (8.5)
- *Renal Impairment:* Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment. (8.6)
- *Hepatic Impairment:* Subjects with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz is not recommended for use in these patients. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [02/2011]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Toviaz® is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

2 DOSAGE AND ADMINISTRATION

The recommended starting dose of Toviaz is 4 mg once daily. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily.

The daily dose of Toviaz should not exceed 4 mg in the following populations:

- Patients with severe renal impairment (CL_{CR} <30 mL/min).
- Patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin.

Toviaz is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) [*see **WARNINGS AND PRECAUTIONS** (5.4, 5.6, 5.7); **USE IN SPECIFIC POPULATIONS** (8.6, 8.7); and **DRUG INTERACTIONS** (7.2)*].

Toviaz should be taken with liquid and swallowed whole. Toviaz can be administered with or without food, and should not be chewed, divided, or crushed.

3 DOSAGE FORMS AND STRENGTHS

Toviaz (fesoterodine fumarate) extended-release tablets 4 mg are light blue, oval, biconvex, film-coated, and engraved with "FS" on one side.

Toviaz (fesoterodine fumarate) extended-release tablets 8 mg are blue, oval, biconvex, film-coated, and engraved with "FT" on one side.

4 CONTRAINDICATIONS

Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients, or to tolterodine tartrate tablets or tolterodine tartrate extended-release capsules. [*see **MECHANISM OF ACTION** (12.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Angioedema: Angioedema of the face, lips, tongue, and/or larynx has been reported with fesoterodine. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, fesoterodine should be promptly discontinued and appropriate therapy and/or measures to ensure a patent airway should be promptly provided.

5.2 Bladder Outlet Obstruction: Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention [*see **CONTRAINDICATIONS** (4)*].

5.3 Decreased Gastrointestinal Motility: Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

5.4 Controlled Narrow-Angle Glaucoma: Toviaz should be used with caution in patients being treated for narrow-angle glaucoma, and only where the potential benefits outweigh the risks [*see **CONTRAINDICATIONS** (4)*].

5.5 Hepatic Impairment: Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population [*see **USE IN SPECIFIC POPULATIONS** (8.7) and **DOSAGE AND ADMINISTRATION** (2)*].

5.6 Renal Impairment: Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment [*see **USE IN SPECIFIC POPULATIONS** (8.6) and **DOSAGE AND ADMINISTRATION** (2)*].

5.7 Concomitant Administration with CYP3A4 Inhibitors: Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin).

In patients taking weak or moderate CYP3A4 inhibitors (e.g., erythromycin), careful assessment of tolerability at the 4 mg daily dose is advised prior to increasing the daily dose to 8 mg. While this specific interaction potential was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with potent CYP3A4 inhibitors [*see **DRUG INTERACTIONS** (7.2) and **DOSAGE AND ADMINISTRATION** (2)*].

5.8 Myasthenia Gravis: Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder, of which 2288 were treated with fesoterodine. Of this total, 782 received Toviaz 4 mg/day, and 785 received Toviaz 8 mg/day in Phase 2 or 3 studies with treatment periods of 8 or 12 weeks. Approximately 80% of these patients had >10 weeks exposure to Toviaz in these trials.

A total of 1964 patients participated in two 12-week, Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these two studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day.

In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be not related or unlikely to be related to study medication by the investigator, except for

four patients receiving Toviaz who reported one serious adverse event each: angina, chest pain, gastroenteritis, and QT prolongation on ECG.

The most commonly reported adverse event in patients treated with Toviaz was dry mouth. The incidence of dry mouth was higher in those taking 8 mg/day (35%) and in those taking 4 mg/day (19%), as compared to placebo (7%). Dry mouth led to discontinuation in 0.4%, 0.4%, and 0.8% of patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg, respectively. For those patients who reported dry mouth, most had their first occurrence of the event within the first month of treatment.

The second most commonly reported adverse event was constipation. The incidence of constipation was 2% in those taking placebo, 4% in those taking 4 mg/day, and 6% in those taking 8 mg/day.

Table 1 lists adverse events, regardless of causality, that were reported in the combined Phase 3, randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with Toviaz 4 or 8 mg once daily for up to 12 weeks.

Table 1: Adverse events with an incidence exceeding the placebo rate and reported by ≥1% of patients from double-blind, placebo-controlled Phase 3 trials of 12 weeks treatment duration

System organ class/Preferred term	Placebo N=554 %	Toviaz 4 mg/day N=554 %	Toviaz 8 mg/day N=566 %
Gastrointestinal disorders			
Dry mouth	7.0	18.8	34.6
Constipation	2.0	4.2	6.0
Dyspepsia	0.5	1.6	2.3
Nausea	1.3	0.7	1.9
Abdominal pain upper	0.5	1.1	0.5
Infections			
Urinary tract infection	3.1	3.2	4.2
Upper respiratory tract infection	2.2	2.5	1.8
Eye disorders			
Dry eyes	0	1.4	3.7
Renal and urinary disorders			
Dysuria	0.7	1.3	1.6
Urinary retention	0.2	1.1	1.4
Respiratory disorders			
Cough	0.5	1.6	0.9
Dry throat	0.4	0.9	2.3
General disorders			
Edema peripheral	0.7	0.7	1.2
Musculoskeletal disorders			
Back pain	0.4	2.0	0.9
Psychiatric disorders			
Insomnia	0.5	1.3	0.4
Investigations			
ALT increased	0.9	0.5	1.2
GGT increased	0.4	0.4	1.2
Skin disorders			
Rash	0.5	0.7	1.1

ALT = alanine aminotransferase; GGT = gamma glutamyltransferase

Patients also received Toviaz for up to three years in open-label extension phases of one Phase 2 and two Phase 3 controlled trials. In all open-label trials combined, 857, 701, 529, and 105 patients received Toviaz for at least 6 months, 1 year, 2 years, and 3 years, respectively. The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, dry eyes, dyspepsia, and abdominal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator and reported more than once during the open-label

treatment period of up to 3 years, included urinary retention (3 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

6.2 Post-marketing Experience

The following events have been reported in association with fesoterodine use in worldwide post-marketing experience: *Eye disorders:* Blurred vision; *Cardiac disorders:* Palpitations; *General disorders and administrative site conditions:* hypersensitivity reactions, including angioedema with airway obstruction, face edema.

Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of fesoterodine in their causation cannot be reliably determined.

7 DRUG INTERACTIONS

7.1 Antimuscarinic Drugs: Coadministration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

7.2 CYP3A4 Inhibitors: Doses of Toviaz greater than 4mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. Coadministration of the potent CYP3A4 inhibitor ketoconazole with fesoterodine led to approximately a doubling of the maximum concentration (C_{max}) and area under the concentration versus time curve (AUC) of 5-hydroxymethyl tolterodine (5-HMT), the active metabolite of fesoterodine. Compared with CYP2D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole [*see **CLINICAL PHARMACOLOGY** (12.3), **WARNINGS AND PRECAUTIONS** (5.7), and **DOSAGE AND ADMINISTRATION** (2)*].

The effects of weak or moderate CYP3A4 inhibitors were not examined.

7.3 CYP3A4 Inducers: No dosing adjustments are recommended in the presence of CYP3A4 inducers, such as rifampin and carbamazepine. Following induction of CYP3A4 by coadministration of rifampin 600 mg once a day, C_{max} and AUC of the active metabolite of fesoterodine decreased by approximately 70% and 75%, respectively, after oral administration of Toviaz 8 mg. The terminal half-life of the active metabolite was not changed.

7.4 CYP2D6 Inhibitors: The interaction with CYP2D6 inhibitors was not tested clinically. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, C_{max} and AUC of the active metabolite are increased 1.7- and 2-fold, respectively.

No dosing adjustments are recommended in the presence of CYP2D6 inhibitors.

7.5 Drugs Metabolized by Cytochrome P450: *In vitro* data indicate that at therapeutic concentrations, the active metabolite of fesoterodine does not have the potential to inhibit or induce Cytochrome P450 enzyme systems [see CLINICAL PHARMACOLOGY (12.3)].

7.6 Oral Contraceptives: In the presence of fesoterodine, there are no clinically significant changes in the plasma concentrations of combined oral contraceptives containing ethinyl estradiol and levonorgestrel [see CLINICAL PHARMACOLOGY (12.3)].

7.7 Drug-Laboratory Test Interactions: Interactions between Toviaz and laboratory tests have not been studied.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies using Toviaz in pregnant women.

No dose-related teratogenicity was observed in reproduction studies performed in mice and rabbits. In mice at 6 to 27 times the expected exposure at the maximum recommended human dose (MRHD) of 8 mg based on AUC (75 mg/kg/day, oral), increased resorptions and decreased live fetuses were observed. One fetus with cleft palate was observed at each dose (15, 45, and 75 mg/kg/day), at an incidence within the background historical range. In rabbits treated at 3 to 11 times the MRHD (27 mg/kg/day, oral), incompletely ossified sternebrae (retardation of bone development) were observed in fetuses. In rabbits at 9 to 11 times the MRHD (4.5 mg/kg/day, subcutaneous), maternal toxicity and incompletely ossified sternebrae were observed in fetuses (at an incidence within the background historical range). In rabbits at 3 times the MRHD (1.5 mg/kg/day, subcutaneous), decreased maternal food consumption in the absence of any fetal effects was observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and reproduction of the F_1 dams or on the F_2 offspring.
Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

8.3 Nursing Mothers: It is not known whether fesoterodine is excreted in human milk. Toviaz should not be administered during nursing unless the potential benefit outweighs the potential risk to the neonate.

8.4 Pediatric Use: The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients. The safety and effectiveness of Toviaz in pediatric patients have not been established.

8.5 Geriatric Use: No dose adjustment is recommended for the elderly. The pharmacokinetics of fesoterodine are not significantly influenced by age.

Of 1567 patients who received Toviaz 4 mg/day or 8 mg/day in the Phase 2 and 3, placebo-controlled, efficacy and safety studies, 515 (33%) were 65 years of age or older, and 140 (9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies; however, the incidence of antimuscarinic adverse events, including dry mouth, constipation, dyspepsia, increase in residual urine, dizziness (at 8 mg only) and urinary tract infection, was higher in patients 75 years of age and older as compared to younger patients [*see **CLINICAL STUDIES (14) and ADVERSE REACTIONS (6)***].

8.6 Renal Impairment: In patients with severe renal impairment (CL_{CR} < 30 mL/min), C_{max} and AUC are increased 2.0- and 2.3-fold, respectively. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment. In patients with mild or moderate renal impairment (CL_{CR} ranging from 30-80 mL/min), C_{max} and AUC of the active metabolite are increased up to 1.5- and 1.8-fold respectively, as

compared to healthy subjects. No dose adjustment is recommended in patients with mild or moderate renal impairment [*see **WARNINGS AND PRECAUTIONS** (5.5) and **DOSAGE AND ADMINISTRATION** (2)*].

8.7 Hepatic Impairment: Patients with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz is not recommended for use in these patients. In patients with moderate (Child-Pugh B) hepatic impairment, C_{max} and AUC of the active metabolite are increased 1.4- and 2.1-fold, respectively, as compared to healthy subjects. No dose adjustment is recommended in patients with mild or moderate hepatic impairment [*see **WARNINGS AND PRECAUTIONS** (5.4) and **DOSAGE AND ADMINISTRATION** (2)*].

8.8 Gender: No dose adjustment is recommended based on gender. The pharmacokinetics of fesoterodine are not significantly influenced by gender.

8.9 Race: Available data indicate that there are no differences in the pharmacokinetics of fesoterodine between Caucasian and Black healthy subjects following administration of Toviaz.

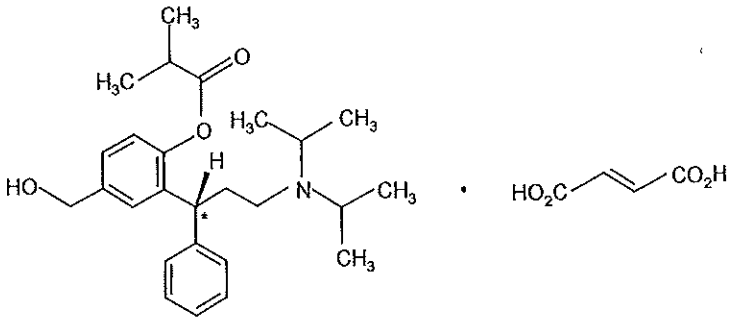
10 OVERDOSAGE

Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

11 DESCRIPTION

Toviaz contains fesoterodine fumarate and is an extended-release tablet. Fesoterodine is rapidly de-esterified to its active metabolite (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol, or 5-hydroxymethyl tolterodine, which is a muscarinic receptor antagonist.

Chemically, fesoterodine fumarate is designated as isobutyric acid 2-((R)-3-diisopropylammonium-1-phenylpropyl)-4-(hydroxymethyl) phenyl ester hydrogen fumarate. The empirical formula is $C_{30}H_{41}NO_7$ and its molecular weight is 527.66. The structural formula is:



The asterisk (*) indicates the chiral carbon.

Fesoterodine fumarate is a white to off-white powder, which is freely soluble in water. Each Toviaz extended-release tablet contains either 4 mg or 8 mg of fesoterodine fumarate and the following inactive ingredients: glyceryl behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action:

Fesoterodine is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine, which is responsible for the antimuscarinic activity of fesoterodine and is also one of the active moieties of tolterodine tartrate tablets and tolterodine tartrate extended release capsules.

Muscarinic receptors play a role in contractions of urinary bladder smooth muscle and stimulation of salivary secretion. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.

12.2 Pharmacodynamics:

In a urodynamic study involving patients with involuntary detrusor contractions, the effects after the administration of fesoterodine on the volume at first detrusor contraction and bladder capacity were assessed. Administration of fesoterodine increased the volume at first detrusor contraction and bladder capacity in a dose-dependent manner. These findings are consistent with an antimuscarinic effect on the bladder.

Cardiac Electrophysiology: The effect of fesoterodine 4 mg and 28 mg on the QT interval was evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg once a day) parallel trial with once-daily treatment over a period of 3 days in 261 male and female subjects aged 44 to 65 years. Electrocardiographic parameters were measured over a 24-hour period at pre-dose, after the first administration, and after the third administration of study medication. Fesoterodine 28 mg was chosen because this dose, when administered to CYP2D6 extensive metabolizers, results in an exposure to the active metabolite that is similar to the exposure in a CYP2D6 poor metabolizer receiving fesoterodine 8 mg together with CYP3A4 blockade. Corrected QT intervals (QTc) were calculated using Fridericia's correction and a linear individual correction method. Analyses of 24-hour average QTc, time-matched baseline-corrected QTc, and time-matched placebo-subtracted QTc intervals indicate that fesoterodine at doses of 4 and 28 mg/day did not prolong the QT interval. The sensitivity of the study was confirmed by positive QTc prolongation by moxifloxacin.

Toviaz is associated with an increase in heart rate that correlates with increasing dose. In the study described above, when compared to placebo, the mean increase in heart rate associated with a dose of 4 mg/day and 28 mg/day of fesoterodine was 3 beats/minute and 11 beats/minute, respectively.

In the two, phase 3, placebo-controlled studies in patients with overactive bladder, the mean increase in heart rate compared to placebo was approximately 3-4 beats/minute in the 4 mg/day group and 3-5 beats/minute in the 8 mg/day group.

12.3 Pharmacokinetics:

Absorption: After oral administration, fesoterodine is well absorbed. Due to rapid and extensive hydrolysis by nonspecific esterases to its active metabolite 5-hydroxymethyl tolterodine, fesoterodine cannot be detected in plasma. Bioavailability of the active metabolite is 52%. After single or multiple-dose oral administration of fesoterodine in doses from 4 mg to 28 mg, plasma concentrations of the active metabolite are proportional to the dose. Maximum plasma levels are reached after approximately 5 hours. No accumulation occurs after multiple-dose administration.

A summary of pharmacokinetic parameters for the active metabolite after a single dose of Toviaz 4 mg and 8 mg in extensive and poor metabolizers of CYP2D6 is provided in Table 2.

Table 2: Summary of geometric mean [CV] pharmacokinetic parameters for the active metabolite after a single dose of Toviaz 4 mg and 8 mg in extensive and poor CYP2D6 metabolizers

	Toviaz 4 mg		Toviaz 8 mg	
Parameter	**EM (n=16)**	**PM (n=8)**	**EM (n=16)**	**PM (n=8)**
C_{max} (ng/mL)	1.89 [43%]	3.45 [54%]	3.98 [28%]	6.90 [39%]
$AUC_{0\text{-}tz}$ (ng*h/mL)	21.2 [38%]	40.5 [31%]	45.3 [32%]	88.7 [36%]
t_{max} (h)[a]	5 [2-6]	5 [5-6]	5 [3-6]	5 [5-6]
$t_{½}$ (h)	7.31 [27%]	7.31 [30%]	8.59 [41%]	7.66 [21%]

EM = extensive CYP2D6 metabolizer, PM = poor CYP2D6 metabolizer, CV = coefficient of variation

C_{max} = maximum plasma concentration, $AUC_{0\text{-}tz}$ = area under the concentration time curve from zero up to the last measurable plasma concentration, t_{max} = time to reach C_{max}, $t_{½}$ = terminal half-life

[a] Data presented as median (range)

Effect of Food: There is no clinically relevant effect of food on the pharmacokinetics of fesoterodine. In a study of the effects of food on the pharmacokinetics of fesoterodine in 16 healthy male volunteers, concomitant food intake increased the active metabolite of fesoterodine AUC by approximately 19% and C_{max} by 18% [*see **DOSAGE AND ADMINISTRATION (2)**]*.

Distribution: Plasma protein binding of the active metabolite is low (approximately 50%) and is primarily bound to albumin and alpha-1-acid glycoprotein. The mean steady-state volume of distribution following intravenous infusion of the active metabolite is 169 L.

Metabolism: After oral administration, fesoterodine is rapidly and extensively hydrolyzed to its active metabolite. The active metabolite is further metabolized in the liver to its carboxy, carboxy-N-desisopropyl, and N-desisopropyl metabolites via two major pathways involving CYP2D6 and CYP3A4. None of these metabolites contribute significantly to the antimuscarinic activity of fesoterodine.

Variability in CYP2D6 Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6. C_{max} and AUC of the active metabolite are increased 1.7- and 2-fold, respectively, in CYP2D6 poor metabolizers, as compared to extensive metabolizers.

Excretion: Hepatic metabolism and renal excretion contribute significantly to the elimination of the active metabolite. After oral administration of fesoterodine, approximately 70% of the administered dose was recovered in urine as the active metabolite (16%), carboxy metabolite (34%), carboxy-N-desisopropyl metabolite (18%), or N-desisopropyl metabolite (1%), and a smaller amount (7%) was recovered in feces.

The terminal half-life of the active metabolite is approximately 4 hours following an intravenous administration. The apparent terminal half-life following oral administration is approximately 7 hours.

Pharmacokinetics in Specific Populations:

Geriatric Patients: Following a single 8 mg oral dose of fesoterodine, the mean (±SD) AUC and C_{max} for the active metabolite 5-hydroxymethyl tolterodine in 12 elderly men (mean age 67 years) were 51.8 ± 26.1 h*ng/mL and 3.8 ± 1.7 ng/mL, respectively. In the same study, the mean (±SD) AUC and C_{max} in 12 young men (mean age 30 years) were 52.0 ± 31.5 h*ng/mL and 4.1 ± 2.1 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by age [*see **USE IN SPECIFIC POPULATIONS** (8.5)*].

Pediatric Patients: The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients [*see **USE IN SPECIFIC POPULATIONS** (8.4)*].

Gender: Following a single 8 mg oral dose of fesoterodine, the mean (±SD) AUC and C_{max} for the active metabolite 5-hydroxymethyl tolterodine in 12 elderly men (mean age 67 years) were 51.8 ± 26.1 h*ng/mL and 3.8 ± 1.7 ng/mL, respectively. In the same study, the mean (±SD) AUC and C_{max} in 12 elderly women (mean age 68 years) were 56.0 ± 28.8 h*ng/mL and 4.6 ± 2.3 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by gender [*see **USE IN SPECIFIC POPULATIONS** (8.8)*].

Race: The effects of Caucasian or Black race on the pharmacokinetics of fesoterodine were examined in a study of 12 Caucasian and 12 Black African young male volunteers. Each subject received a single oral dose of 8mg fesoterodine. The mean (±SD) AUC and C_{max} for the active metabolite 5-hydroxymethyl tolterodine in Caucasian males were 73.0 ± 27.8 h*ng/mL and 6.1 ± 2.7 ng/mL, respectively. The mean (±SD) AUC and C_{max} in Black males were 65.8 ± 23.2 h*ng/mL and 5.5 ± 1.9 ng/mL, respectively. The pharmacokinetics of fesoterodine were not significantly influenced by race [*see **USE IN SPECIFIC POPULATIONS** (8.9)*].

Renal Impairment: In patients with mild or moderate renal impairment (CL_{CR} ranging from 30-80 mL/min), C_{max} and AUC of the active metabolite are increased up to 1.5- and 1.8-fold respectively, as compared to healthy subjects. In patients with severe renal impairment (CL_{CR} < 30 mL/min), C_{max} and AUC are increased 2.0- and 2.3-fold, respectively.

In patients with mild or moderate renal impairment, no dose adjustment is recommended. Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment [*see **USE IN SPECIFIC POPULATIONS** (8.6), **WARNINGS AND PRECAUTIONS** (5.5), and **DOSAGE AND ADMINISTRATION** (2)*].

Hepatic Impairment: In patients with moderate (Child-Pugh B) hepatic impairment, C_{max} and AUC of the active metabolite are increased 1.4- and 2.1-fold, respectively, as compared to healthy subjects.

No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Subjects with severe hepatic impairment (Child-Pugh C) have not been studied; therefore Toviaz is not recommended for use in these patients [*see **USE IN SPECIFIC POPULATIONS** (8.7), **WARNINGS AND PRECAUTIONS** (5.4), and **DOSAGE AND ADMINISTRATION** (2)*].

Drug-Drug Interactions:

Drugs Metabolized by Cytochrome P450: At therapeutic concentrations, the active metabolite of fesoterodine does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 *in vitro*[*see **DRUG INTERACTIONS** (7.5)*].

CYP3A4 Inhibitors: Following blockade of CYP3A4 by coadministration of the potent CYP3A4 inhibitor ketoconazole 200 mg twice a day for 5 days, C_{max} and AUC of the active metabolite of fesoterodine increased 2.0- and 2.3-fold, respectively, after oral administration of Toviaz 8 mg to CYP2D6 extensive metabolizers. In CYP2D6 poor metabolizers, C_{max} and AUC of the active metabolite of fesoterodine increased 2.1- and 2.5-fold,

respectively, during coadministration of ketoconazole 200 mg twice a day for 5 days. C_{max} and AUC were 4.5- and 5.7-fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole. In a separate study coadministering fesoterodine with ketoconazole 200 mg once a day for 5 days, the C_{max} and AUC values of the active metabolite of fesoterodine were increased 2.2-fold in CYP2D6 extensive metabolizers and 1.5- and 1.9-fold, respectively, in CYP2D6 poor metabolizers. C_{max} and AUC were 3.4- and 4.2-fold higher, respectively, in subjects who were CYP2D6 poor metabolizers and taking ketoconazole compared to subjects who were CYP2D6 extensive metabolizers and not taking ketoconazole.

Therefore, doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin [*see **DRUG INTERACTIONS** (7.2)*], ***WARNINGS AND PRECAUTIONS** (5.6), and **DOSAGE AND ADMINISTRATION** (2)*].

The effects of weak or moderate CYP3A4 inhibitors were not examined.

CYP3A4 Inducers: Following induction of CYP3A4 by coadministration of rifampicin 600 mg once a day, C_{max} and AUC of the active metabolite of fesoterodine decreased by approximately 70% and 75%, respectively, after oral administration of Toviaz 8 mg. The terminal half-life of the active metabolite was not changed.

Induction of CYP3A4 may lead to reduced plasma levels. No dosing adjustments are recommended in the presence of CYP3A4 inducers [*see **DRUG INTERACTIONS** (7.3)*].

CYP2D6 Inhibitors: The interaction with CYP2D6 inhibitors was not studied. In poor metabolizers for CYP2D6, representing a maximum CYP2D6 inhibition, C_{max} and AUC of the active metabolite are increased 1.7- and 2-fold, respectively.

No dosing adjustments are recommended in the presence of CYP2D6 inhibitors [*see **DRUG INTERACTIONS** (7.4)*].

Oral Contraceptives: Thirty healthy female subjects taking an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel were evaluated in a 2-period crossover study. Each subject was randomized to receive concomitant administration of either placebo or fesoterodine 8 mg once daily on days 1 – 14 of hormone cycle for 2 consecutive cycles. Pharmacokinetics of ethinyl estradiol and levonorgestrel were assessed on day 13 of each cycle. Fesoterodine increased the AUC and C_{max} of ethinyl estradiol by 1 – 3% and decreased the AUC and C_{max} of levonorgestrel by 11 – 13% [*see **DRUG INTERACTIONS** (7.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related carcinogenicity was found in 24-month studies with oral administration to mice and rats. The highest tolerated doses in mice (females 45 to 60 mg/kg/day, males 30 to 45 mg/kg/day) correspond to 11to19 times (females) and 4 to 9 times (males) the estimated human AUC values reached with fesoterodine 8 mg, which is the Maximum Recommended Human Dose (MRHD). In rats, the highest tolerated dose (45 to 60 mg/kg/day) corresponds to 3 to 8 times (females) and 3 to 14 times (males) the estimated human AUC at the MRHD.

Fesoterodine was not mutagenic or genotoxic *in vitro* (Ames tests, chromosome aberration tests) or *in vivo* (mouse micronucleus test).

Fesoterodine had no effect on reproductive function, fertility, or early embryonic development of the fetus at non-maternally toxic doses in mice. The maternal No-Observed-Effect Level (NOEL) and the NOEL for effects on reproduction and early embryonic development were both 15 mg/kg/day. Based on AUC, the systemic exposure was 0.6 to 1.5 times higher in mice than in humans at the MRHD, whereas based on peak plasma concentrations, the exposure in mice was 5 to 9 times higher. The Lowest-Observed-Effect Level (LOEL) for maternal toxicity was 45 mg/kg/day.

14 CLINICAL STUDIES

Toviaz extended-release tablets were evaluated in two, Phase 3, randomized, double-blind, placebo-controlled, 12-week studies for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. Entry criteria required that patients have symptoms of overactive bladder for $\geq$ 6-months duration, at least 8 micturitions per day, and at least 6 urinary urgency episodes or 3 urge incontinence episodes per 3-day diary period. Patients were randomized to a fixed dose of Toviaz 4 or 8 mg/day or placebo. In one of these studies, 290 patients were randomized to an active control arm (an oral antimuscarinic agent). For the combined studies, a total of 554 patients received placebo, 554 patients received Toviaz 4 mg/day, and 566 patients received Toviaz 8 mg/day. The majority of patients were Caucasian (91%) and female (79%) with a mean age of 58 years (range 19-91 years).

The primary efficacy endpoints were the mean change in the number of urge urinary incontinence episodes per 24 hours and the mean change in the number of micturitions (frequency) per 24 hours. An important secondary endpoint was the mean change in the voided volume per micturition.

Results for the primary endpoints and for mean change in voided volume per micturition from the two 12-week clinical studies of Toviaz are reported in Table 3.

Table 3: Mean baseline and change from baseline to Week 12 for urge urinary incontinence episodes, number of micturitions, and volume voided per micturition

Parameter	Study 1			Study 2		
	Placebo N=279	Toviaz 4mg/day N=265	Toviaz 8mg/day N=276	Placebo N=266	Toviaz 4mg/day N=267	Toviaz 8mg/day N=267
Number of urge incontinence episodes per 24 hours[a]						
Baseline	3.7	3.8	3.7	3.7	3.9	3.9
Change from baseline	-1.20	-2.06	-2.27	-1.00	-1.77	-2.42
p-value vs. placebo	-	0.001	<0.001	-	<0.003	<0.001
Number of micturitions per 24 hours						
Baseline	12.0	11.6	11.9	12.2	12.9	12.0
Change from baseline	-1.02	-1.74	-1.94	-1.02	-1.86	-1.94
p-value vs. placebo	-	<0.001	<0.001	-	0.032	<0.001
Voided volume per micturition (mL)						
Baseline	150	160	154	159	152	156
Change from baseline	10	27	33	8	17	33
p-value vs. placebo	-	<0.001	<0.001	-	0.150	<0.001

Vs. = versus

[a] Only those patients who were urge incontinent at baseline were included for the analysis of number of urge incontinence episodes per 24 hours: In Study 1, the number of these patients was 211, 199, and 223 in the placebo, Toviaz 4 mg/day and Toviaz 8 mg/day groups, respectively. In Study 2, the number of these patients was 205, 228, and 218, respectively.

Figures 1-4: The following figures show change from baseline over time in number of micturitions and urge urinary incontinence episodes per 24 h in the two studies.

Figure 1: Change in Number of Micturitions per 24 h (Study 1)

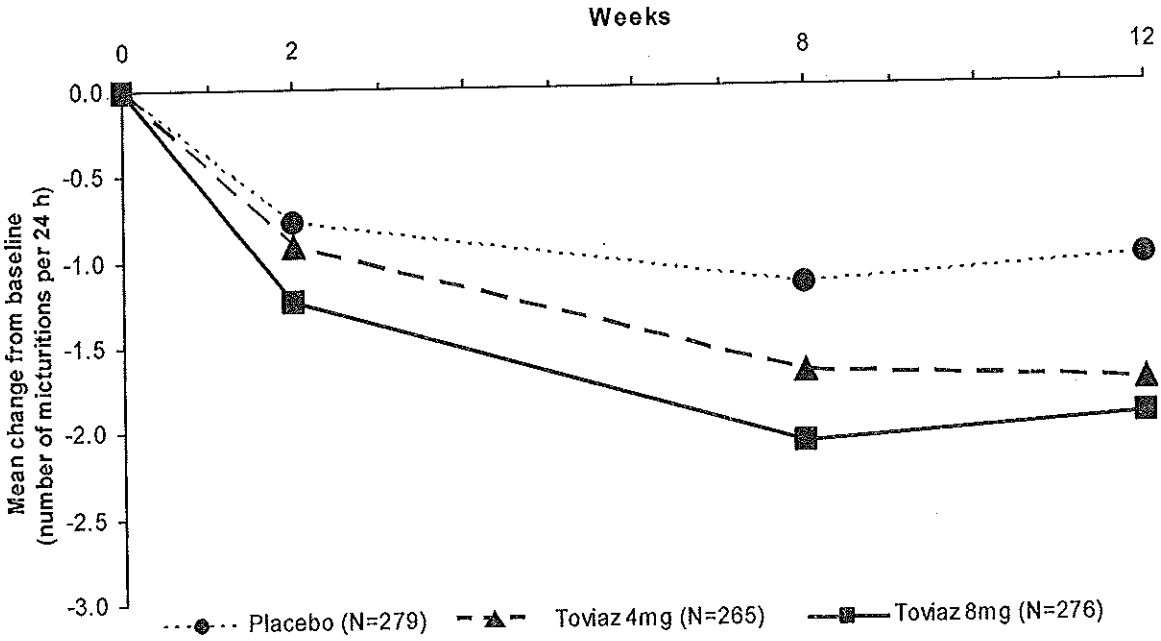


Figure 2: Change in Urge Incontinence Episodes per 24 h (Study 1)

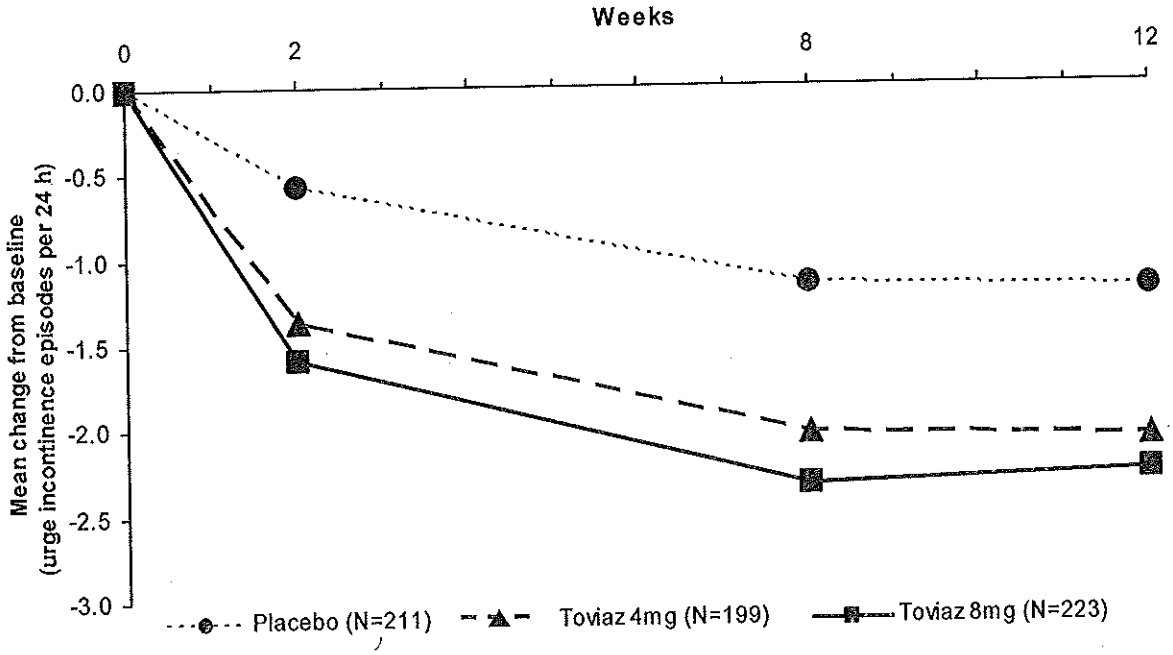


Figure 3: Change in Number of Micturitions per 24 h (Study 2)

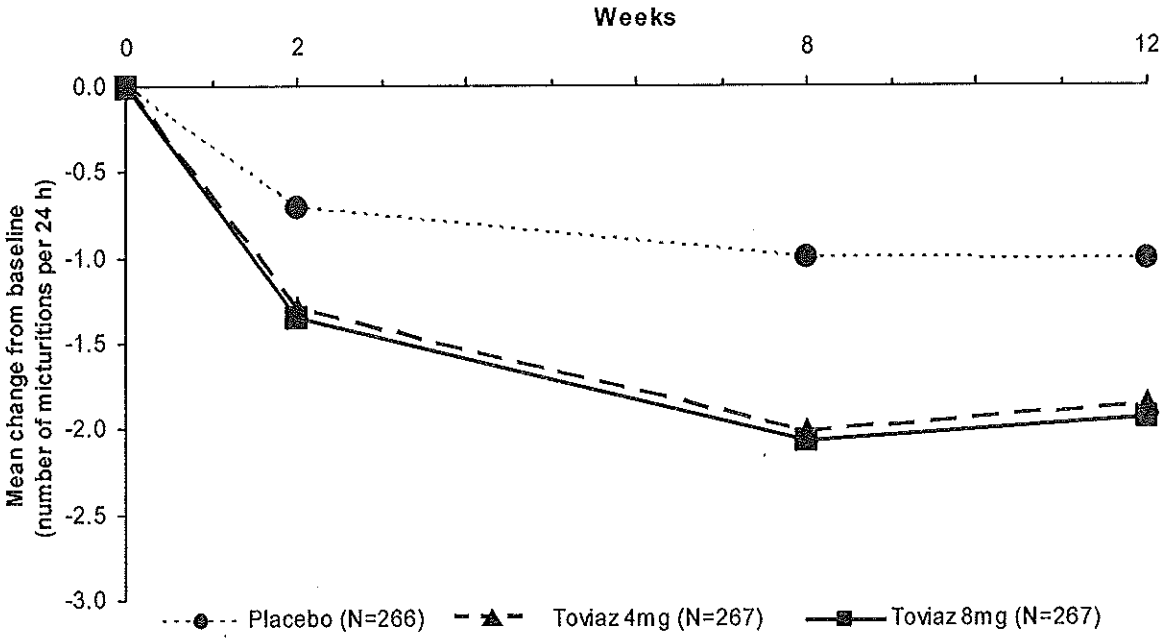
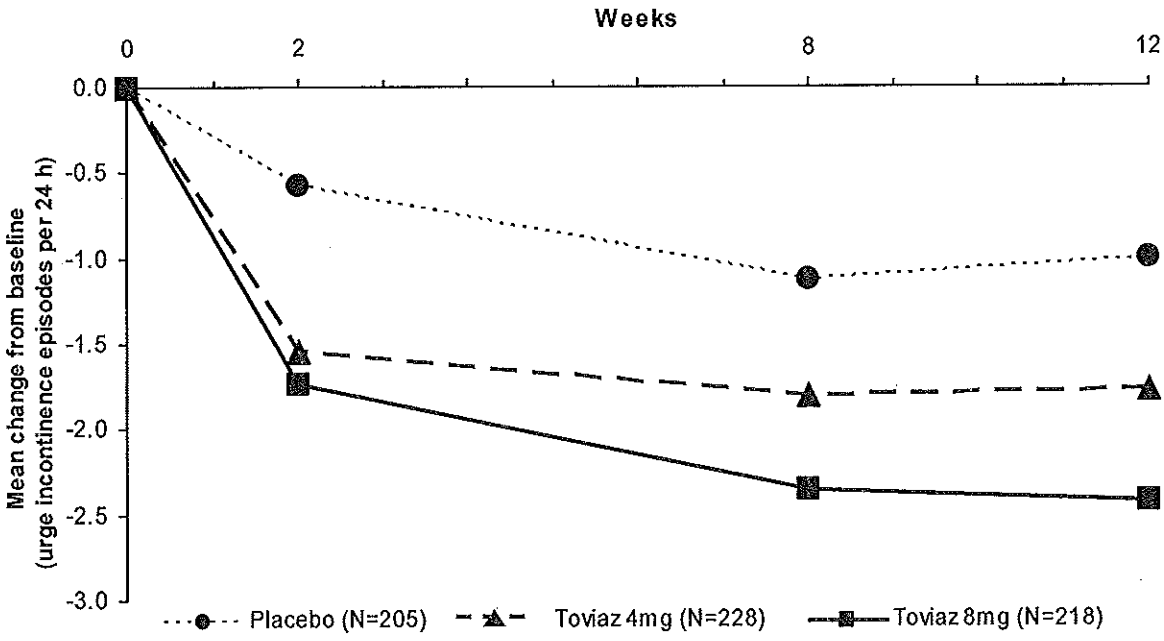


Figure 4: Change in Urge Incontinence Episodes per 24 h (Study 2)



A reduction in number of urge urinary incontinence episodes per 24 hours was observed for both doses as compared to placebo as early as two weeks after starting Toviaz therapy.

16 HOW SUPPLIED/STORAGE AND HANDLING

Toviaz (fesoterodine fumarate) extended-release tablets 4 mg are light blue, oval, biconvex, film-coated, and engraved with "FS" on one side. They are supplied as follows:

Bottles of 30	NDC 0069-0242-30
Bottles of 90	NDC 0069-0242-68
Unit Dose Package of 100	NDC 0069-0242-41

Toviaz (fesoterodine fumarate) extended-release tablets 8 mg are blue, oval, biconvex, film-coated, and engraved with "FT" on one side. They are supplied as follows:

Bottles of 30	NDC 0069-0244-30
Bottles of 90	NDC 0069-0244-68
Unit Dose Package of 100	NDC 0069-0244-41

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2)

17.1 Information for Patients:

Patients should be informed that fesoterodine may produce angioedema, which could result in life-threatening airway obstruction. Patients should be advised to promptly discontinue fesoterodine therapy and seek immediate medical attention if they experience edema of the tongue or laryngopharynx, or difficult breathing.

Patients should be informed that Toviaz, like other antimuscarinic agents, may produce clinically significant adverse effects related to antimuscarinic pharmacological activity including constipation and urinary retention. Toviaz, like other antimuscarinics, may be associated with blurred vision, therefore, patients should be advised to exercise caution until the drug's effects on the patient have been determined. Heat prostration (due to decreased sweating) can occur when Toviaz, like other antimuscarinic drugs, is used in a hot environment.

Patients should also be informed that alcohol may enhance the drowsiness caused by Toviaz, like other anticholinergic agents. Patients should read the patient leaflet entitled "Patient Information TOVIAZ" before starting therapy with Toviaz.

17.2 FDA Approved Patient Labeling

Manufactured by:
SCHWARZ PHARMA PRODUKTIONS-GmbH
08056 Zwickau, Germany

Distributed by:

Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

LAB-0381-6.0
Revised February 2011

Patient Information
TOVIAZ® (TOH-vee-as)
(fesoterodine fumarate)
extended-release tablets

Read the Patient Information that comes with TOVIAZ before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is TOVIAZ?

TOVIAZ is a prescription medicine used in **adults** to treat symptoms of a condition called **overactive bladder**, including:

- Urge urinary incontinence -- leaking or wetting accidents due to a strong need to urinate,
- Urinary urgency -- having a strong need to urinate right away,
- Urinary frequency -- having to urinate too often.

TOVIAZ has not been studied in children.

Who should not take TOVIAZ?

Do not take TOVIAZ if you:

- Are not able to empty your bladder (urinary retention)
- Have delayed or slow emptying of your stomach (gastric retention)
- Have an eye problem called "uncontrolled narrow-angle glaucoma"
- Are allergic to TOVIAZ or any of its ingredients. See the end of this leaflet for a complete list of ingredients
- Are allergic to Detrol® or Detrol® LA, which contains tolterodine.

What should I tell my doctor before starting TOVIAZ?

Before starting TOVIAZ, tell your doctor about all of your medical and other conditions that may affect the use of TOVIAZ, including:

- Stomach or intestinal problems or problems with constipation
- Problems emptying your bladder or if you have a weak urine stream
- Treatment for an eye problem called narrow-angle glaucoma
- Kidney problems
- Liver problems
- A condition called myasthenia gravis
- If you are pregnant or trying to become pregnant. It is not known if TOVIAZ can harm your unborn baby.
- If you are breastfeeding. It is not known if TOVIAZ passes into breast milk or if it can harm your baby. Talk to your doctor about the best way to feed your baby if you take TOVIAZ.

Before starting on TOVIAZ, tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal products. TOVIAZ may affect the way other medicines work, and other medicines may affect how TOVIAZ works. Especially tell your doctor if you are taking antibiotics or antifungal medicines.
Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I take TOVIAZ?

- Take TOVIAZ exactly as your doctor tells you to take it.
- Your doctor may give you the lower 4 mg dose of TOVIAZ if you have certain medical conditions, such as severe kidney problems.
- Take TOVIAZ with liquid and swallow the tablet whole. Do not chew, divide, or crush the tablet.
- You can take TOVIAZ with or without food.
- If you miss a dose of TOVIAZ, begin taking TOVIAZ again the next day. Do not take 2 doses of TOVIAZ in the same day.

If you take too much TOVIAZ, call your doctor or go to an emergency department right away.

What are the possible side effects of TOVIAZ?

TOVIAZ may cause allergic reactions that may be serious. Symptoms of a serious allergic reaction may include swelling of the face, lips, throat or tongue. If you experience these symptoms, you should stop taking TOVIAZ and get emergency medical help right away.

The most common side effects of TOVIAZ are:

- Dry mouth
- Constipation

TOVIAZ may cause other less common side effects, including:

- Dry eyes
- Trouble emptying the bladder

Tell your doctor if you have any side effects that bother you or that do not go away.
Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.
These are not all of the possible side effects of TOVIAZ. For a complete list, ask your doctor.

What else should I keep in mind while taking TOVIAZ?

- Use caution in driving, operating machinery, or doing other dangerous activities until you know how TOVIAZ affects you. Blurred vision and drowsiness are possible side effects of medicines such as TOVIAZ.
- Use caution in hot environments. Decreased sweating and severe heat illness can occur when medicines such as TOVIAZ are used in a hot environment.
- Drinking alcohol while taking medicines such as TOVIAZ may cause increased drowsiness.

How should I store TOVIAZ?

- Store TOVIAZ at room temperature, 68° to 77°F (20° to 25°C); brief periods permitted between 59° to 86°F (15° to 30°C)
- Protect the medicine from moisture by keeping the bottle closed tightly.
- Safely throw away TOVIAZ that is out of date or no longer needed.

Keep TOVIAZ and all medicines out of the reach of children.

General information about TOVIAZ

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Only use TOVIAZ the way your doctor tells you. Do not give TOVIAZ to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TOVIAZ. If you would like more information, talk with your doctor. You can ask your doctor for information about TOVIAZ that is written for healthcare professionals. You can also call 1-877-9-TOVIAZ (1-877-986-8429) or go to www.TOVIAZ.com.

What are the ingredients in TOVIAZ?

Active ingredient: fesoterodine fumarate
Inactive ingredients: glyceryl behenate, hypromellose, indigo carmine aluminum lake, lactose monohydrate, soya lecithin, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and xylitol.

Manufactured by:
SCHWARZ PHARMA PRODUKTIONS-GmbH
08056 Zwickau, Germany

Distributed by:

LAB-0382-5.0
Revised February 2011

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Detrol® LA safely and effectively. See full prescribing information for Detrol LA.

Detrol® LA (tolterodine tartrate extended release capsules)
For oral administration
Initial U.S. Approval: December 2000

INDICATIONS AND USAGE

Detrol LA is an antimuscarinic indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. (1)

DOSAGE AND ADMINISTRATION

- 4 mg capsules taken orally once daily with water and swallowed whole. (2.1)
- 2 mg capsules taken orally once daily with water and swallowed whole in the presence of:
  - mild to moderate hepatic impairment (Child-Pugh class A or B) (2.2)
  - severe renal impairment [Creatinine Clearance (CCr) 10-30 mL/min] (2.2)
  - drugs that are potent CYP3A4 inhibitors. (2.2)
- DETROL LA is not recommended for use in patients with CCr <10 mL/min. (2.2)
- Detrol LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) (2.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 2 mg and 4 mg (3)

CONTRAINDICATIONS

- Urinary retention (4)
- Gastric retention (4)
- Uncontrolled narrow-angle glaucoma (4)

WARNINGS AND PRECAUTIONS

- Urinary Retention: use caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention. (5.1)
- Gastrointestinal Disorders: use caution in patients with gastrointestinal obstructive disorders or decreased gastrointestinal motility because of the risk of gastric retention. (5.2)
- Controlled Narrow-Angle Glaucoma: use caution in patients being treated for narrow-angle glaucoma. (5.3)
- Myasthenia Gravis: use caution in patients with myasthenia gravis. (5.6)
- QT Prolongation: Consider observations from the thorough QT study in clinical decisions to prescribe DETROL LA to patients with a known history of QT prolongation or to patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications (5.7)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥4% and >placebo) were dry mouth, headache, constipation and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Potent CYP3A4 Inhibitors: Co-administration may increase systemic exposure to DETROL LA. Reduce DETROL LA dose to 2 mg once daily. (7.2)
- Other Anticholinergics (antimuscarinics): Concomitant use with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic pharmacological effects. (7.6)

USE IN SPECIFIC POPULATIONS

- *Pregnancy and Lactation:* DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus. DETROL LA should not be administered during nursing. (8.1, 8.3)
- *Pediatric Use:* Efficacy in the pediatric population has not been demonstrated. Safety information from a study of a total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) is available. (8.4)
- *Renal Impairment:* DETROL LA is not recommended for use in patients with CCr <10 mL/min. Dose adjustment in severe renal impairment (CCr: 10-30 mL/min). (8.6)
- *Hepatic Impairment:* Not recommended for use in severe hepatic impairment (Child Pugh Class C). Dose adjustment in mild to moderate hepatic impairment (Child Pugh Class A, B). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
Revised: [12/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DETROL LA Capsules is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency [*see **CLINICAL STUDIES** (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of DETROL LA Capsules is 4 mg once daily with water and swallowed whole.. The dose may be lowered to 2 mg daily based on individual response and tolerability; however, limited efficacy data are available for DETROL LA 2 mg [*see **CLINICAL STUDIES** (14)*].

2.2 Dosage Adjustment in Specific Populations

For patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) or severe renal impairment (CCr 10 - 30 mL/min), the recommended dose of DETROL LA is 2 mg once daily. DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C). Patients with CCr<10 mL/min have not been studied and use of DETROL LA in this population is not recommended [*see **WARNINGS AND PRECAUTIONS (5.4), USE IN SPECIFIC POPULATIONS (8.6, 8.7)***].

2.3 Dosage Adjustment in Presence of Concomitant Drugs

For patients who are taking drugs that are potent inhibitors of CYP3A4 [e.g. ketoconazole, clarithromycin, ritonavir], the recommended dose of DETROL LA is 2 mg once daily [*see **DRUG INTERACTIONS (7.2)***].

3 DOSAGE FORMS AND STRENGTHS

The 2 mg capsules are blue-green with symbol and 2 printed in white ink.
The 4 mg capsules are blue with symbol and 4 printed in white ink.

4 CONTRAINDICATIONS

- urinary retention
- gastric retention
- uncontrolled narrow-angle glaucoma

[*see **WARNINGS AND PRECAUTIONS (5.1), (5.3)***].

5 WARNINGS AND PRECAUTIONS

5.1 Urinary Retention

Administer DETROL LA Capsules with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention. [*see **CONTRAINDICATIONS (4)***].

5.2 Gastrointestinal Disorders

Administer DETROL LA with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention.

DETROL LA, like other antimuscarinic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions associated with decreased gastrointestinal motility (e.g. intestinal atony) [*see **CONTRAINDICATIONS** (4)*].

5.3 Controlled Narrow-Angle Glaucoma

Administer DETROL LA with caution in patients being treated for narrow-angle glaucoma [see ***CONTRAINDICATIONS*** (4)].

5.4 Hepatic Impairment

The clearance of orally administered tolterodine immediate release was substantially lower in cirrhotic patients than in the healthy volunteers. For patients with mild to moderate hepatic impairment (Child-Pugh Class A or B), the recommended dose for DETROL LA is 2 mg once daily. DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) [*see **DOSAGE AND ADMINISTRATION** (2.2) and **USE IN SPECIFIC POPULATIONS** (8.6)*].

5.5 Renal Impairment

Renal impairment can significantly alter the disposition of tolterodine and its metabolites. The dose of DETROL LA should be reduced to 2 mg once daily in patients with severe renal impairment (CCr: 10-30 mL/min). Patients with CCr<10 mL/min have not been studied and use of DETROL LA in this population is not recommended [see ***DOSAGE AND ADMINISTRATION** (2.2), and **USE IN SPECIFIC POPULATIONS** (8.7)*].

5.6 Myasthenia Gravis

Administer DETROL LA with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

5.7 Use in Patients with Congenital or Acquired QT Prolongation

In a study of the effect of tolterodine immediate release tablets on the QT interval [*see **CLINICAL PHARMACOLOGY** (12.2)*] the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs). The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped.

These observations should be considered in clinical decisions to prescribe DETROL LA to patients with a known history of QT prolongation or to patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications. There has been no association of Torsade de Pointes in the international post-marketing experience with DETROL or DETROL LA.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

The efficacy and safety of DETROL LA Capsules was evaluated in 1073 patients (537 assigned to DETROL LA; 536 assigned to placebo) who were treated with 2, 4, 6, or 8 mg/day for up to 15 months. These include a total of 1012 patients (505 randomized to DETROL LA 4 mg once daily and 507 randomized to placebo) enrolled in a randomized, placebo-controlled, double-blind, 12-week clinical efficacy and safety study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

Table 1 lists the adverse events, regardless of causality, that were reported in the randomized, double-blind, placebo-controlled 12-week study at an incidence greater than placebo and in greater than or equal to 1% of patients treated with DETROL LA 4 mg once daily.

Table 1. Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
General	headache	6	5
	fatigue	2	1
Central/Peripheral Nervous	dizziness	2	1
Gastrointestinal	constipation	6	4
	abdominal pain	4	2
	dyspepsia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
Urinary	dysuria	1	0

* in nearest integer.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Dry mouth was the most common adverse event leading to treatment discontinuation among patients receiving DETROL LA [n=12 (2.4%) vs. placebo n=6 (1.2%)].

6.2 Post-marketing Experience

The following events have been reported in association with tolterodine use in worldwide post-marketing experience:

General: anaphylactoid reactions, including angioedema; *Cardiovascular:* tachycardia, palpitations, peripheral edema; *Gastrointestinal:* diarrhea; *Central/Peripheral Nervous:* confusion, disorientation, memory impairment, hallucinations.

Reports of aggravation of symptoms of dementia (e.g., confusion, disorientation, delusion) have been reported after tolterodine therapy was initiated in patients taking cholinesterase inhibitors for the treatment of dementia.

Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

7 DRUG INTERACTIONS

7.1 Potent CYP2D6 Inhibitors

Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in C_{max} and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine [*see **CLINICAL PHARMACOLOGY** (12.1)*]. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered [*see **CLINICAL PHARMACOLOGY** (12.3)*].

7.2 Potent CYP3A4 Inhibitors

Ketoconazole (200 mg daily), a potent CYP3A4 inhibitor, increased the mean C_{max} and AUC of tolterodine by 2- and 2.5-fold, respectively in CYP2D6 poor metabolizers.

For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, clarithromycin or ritonavir, the recommended dose of DETROL LA is 2 mg once daily [*see **DOSAGE AND ADMINISTRATION** (2.2), **CLINICAL PHARMACOLOGY** (12.3)*].

7.3 Other Interactions

No clinically relevant interactions have been observed when tolterodine was co-administered with warfarin, with a combined oral contraceptive drug containing ethinyl estradiol and levonorgestrel, or with diuretics [*see **CLINICAL PHARMACOLOGY** (12.3)*]

7.4 Other drugs metabolized by Cytochrome P450 Isoenzymes

In vivo drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole [*see **CLINICAL PHARMACOLOGY** (12.3)*].

7.5 Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

7.6 Other Anticholinergics

The concomitant use of DETROL LA with other anticholinergic (antimuscarinic) agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision, somnolence and other anticholienrgic pharmacological effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

At approximately 9-12 times the clinical exposure to the pharmacologically active components of DETROL® LA, no anomalies or malformations were observed in mice (based on the AUC of tolterodine and its 5-HMT metabolite at a dose of 20 mg/kg/day). At 14-18 times the exposure (doses of 30 to 40 mg/kg/day) in mice, tolterodine has been shown to be embryolethal and reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification). Pregnant rabbits treated subcutaneously at about 0.3 - 2.5 times the clinical exposure (dose of 0.8 mg/kg/day) did not show any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

8.3 Nursing Mothers

Tolterodine is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced body weight gain. The offspring regained the weight during the maturation phase.

It is not known whether tolterodine is excreted in human milk; therefore, DETROL LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue DETROL LA in nursing mothers.

8.4 Pediatric Use

Efficacy in the pediatric population has not been demonstrated.

The pharmacokinetics of tolterodine extended release capsules have been evaluated in pediatric patients ranging in age from 11–15 years. The dose-plasma concentration relationship was linear over the range of doses assessed. Parent/metabolite ratios differed according to CYP2D6 metabolizer status [*see **CLINICAL PHARMACOLOGY** (12.3)*]. CYP2D6 extensive metabolizers had low serum concentrations of tolterodine and high concentrations of the active metabolite 5-HMT, while poor metabolizers had high concentrations of tolterodine and negligible active metabolite concentrations.

A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5–10 with urinary frequency and urge incontinence were studied in two randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with urinary tract infections was higher in patients treated with DETROL LA (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with DETROL LA compared to 0.9% of children treated with placebo.

8.5 Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine.

In multiple-dose studies in which tolterodine immediate release 4 mg (2 mg bid) was administered, serum concentrations of tolterodine and of 5-HMT were similar in healthy elderly volunteers (aged 64 through 80 years) and healthy young volunteers (aged less than 40 years). In another clinical study, elderly volunteers (aged 71 through 81 years) were given tolterodine immediate release 2 or 4 mg (1 or 2 mg bid). Mean serum concentrations of tolterodine and 5-HMT in these elderly volunteers were approximately 20% and 50% higher, respectively, than concentrations reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger

patients on tolterodine in the Phase 3, 12-week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended.

8.6 Renal Impairment

Renal impairment can significantly alter the disposition of tolterodine immediate release and its metabolites. In a study conducted in patients with creatinine clearance between 10 and 30 mL/min, tolterodine and 5-HMT levels were approximately 2–3 fold higher in patients with renal impairment than in healthy volunteers. Exposure levels of other metabolites of tolterodine (e.g., tolterodine acid, *N*-dealkylated tolterodine acid, *N*-dealkylated tolterodine and *N*-dealkylated hydroxy tolterodine) were significantly higher (10–30 fold) in renally impaired patients as compared to the healthy volunteers. The recommended dose for patients with severe renal impairment (CCr: 10-30 mL/min) is DETROL LA 2 mg daily. Patients with CCr<10 mL/min have not been studied and use of DETROL LA in this population is not recommended [*see **DOSAGE AND ADMINISTRATION** (2.2)* and ***WARNINGS and PRECAUTIONS** (5.5)*]. DETROL LA has not been studied in patients with mild to moderate renal impairment [CCr 30-80 mL/min].

8.7 Hepatic Impairment

Liver impairment can significantly alter the disposition of tolterodine immediate release. In a study of tolterodine immediate release conducted in cirrhotic patients (Child-Pugh Class A and B), the elimination halflife of tolterodine immediate release was longer in cirrhotic patients (mean, 7.8 hours) than in healthy, young, and elderly volunteers (mean, 2 to 4 hours). The clearance of orally administered tolterodine immediate release was substantially lower in cirrhotic patients (1.0 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg). The recommended dose for patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) is DETROL LA 2 mg once daily. DETROL LA is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) [*see **DOSAGE AND ADMINISTRATION** (2.2)* and ***WARNINGS AND PRECAUTIONS** (5.4)*].

8.8 Gender

The pharmacokinetics of tolterodine immediate release and 5-HMT are not influenced by gender. Mean C_{max} of tolterodine immediate release (1.6 µg/L in males versus 2.2 µg/L in females) and the active 5-HMT (2.2 µg/L in males versus 2.5 µg/L in females) are similar in males and females who were administered tolterodine immediate release 2 mg. Mean AUC values of tolterodine (6.7 µg·h/L in males versus 7.8 µg·h/L in females) and 5-HMT (10 µg·h/L in males versus 11 µg·h/L in females) are also similar. The elimination half-life of tolterodine immediate release for both males and females is 2.4 hours, and the half-life of 5-HMT is 3.0 hours in females and 3.3 hours in males.

8.9 Race

Pharmacokinetic differences due to race have not been established.

10 OVERDOSAGE

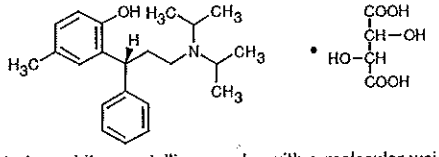
Overdosage with DETROL LA Capsules can potentially result in severe central anticholinergic effects and should be treated accordingly.

ECG monitoring is recommended in the event of overdosage. In dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated [*see **WARNINGS AND PRECAUTIONS** (5.6)* and ***CLINICAL PHARMACOLOGY** (12.2)*].

A 27-month-old child who ingested 5 to 7 tolterodine immediate release 2 mg tablets was treated with a suspension of activated charcoal and was hospitalized overnight with symptoms of dry mouth. The child fully recovered.

11 DESCRIPTION

DETROL LA Capsules contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-N, N-diisopropyl-3-(2-hydroxy-5- methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$. Its structure is:



Tolterodine tartrate is a white, crystalline powder with a molecular weight of 475.6.. The pK_a value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3.

DETROL LA 4 mg capsule for oral administration contains 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C Blue #2.

DETROL LA 2 mg capsule for oral administration contains 2 mg of tolterodine tartrate, and the following inactive ingredients: sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, yellow iron oxide, and FD&C Blue #2.

Both the 2 mg and 4 mg capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tolterodine acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

After oral administration, tolterodine is metabolized in the liver, resulting in the formation of 5-hydroxymethyl tolterodine (5-HMT), the major pharmacologically active metabolite. 5-HMT, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and 5-HMT exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels.

12.2 Pharmacodynamics

Tolterodine has a pronounced effect on bladder function. Effects on urodynamic parameters before and 1 and 5 hours after a single 6.4-mg dose of tolterodine immediate release were determined in healthy volunteers. The main effects of tolterodine at 1 and 5 hours were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. These findings are consistent with an antimuscarinic action on the lower urinary tract.

Cardiac Electrophysiology

The effect of 2 mg BID and 4 mg BID of DETROL immediate release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18–55 years. Study subjects [approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs)] completed sequential 4-day periods of dosing with moxifloxacin 400 mg QD, tolterodine 2 mg BID, tolterodine 4 mg BID, and placebo. The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon coadministration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers [*see **DRUG INTERACTIONS** (7.2)*]. QT interval was measured over a 12-hour period following dosing, including the time of peak plasma concentration (T_{max}) of tolterodine and at steady state (Day 4 of dosing).

Table 2 summarizes the mean change from baseline to steady state in corrected QT interval (QT_c) relative to placebo at the time of peak tolterodine (1 hour) and moxifloxacin (2 hour) concentrations. Both Fridericia's (QT_cF) and a population-specific (QT_cP) method were used to correct QT interval for heart rate. No single QT correction method is known to be more valid than others. QT interval was measured manually and by machine, and data from both are presented. The mean increase of heart rate associated with a 4 mg/day dose of tolterodine in this study was 2.0 beats/minute and 6.3 beats/minute with 8 mg/day tolterodine. The change in heart rate with moxifloxacin was 0.5 beats/minute.

Table 2. Mean (CI) change in QT_c from baseline to steady state (Day 4 of dosing) at T_{max} (relative to placebo)

Drug/Dose	N	QT_cF (msec) (manual)	QT_cF (msec) (machine)	QT_cP (msec) (manual)	QT_cP (msec) (machine)
Tolterodine 2 mg BID*	48	5.01 (0.28, 9.74)	1.16 (-2.99, 5.30)	4.45 (-0.37, 9.26)	2.00 (-1.81, 5.81)
Tolterodine 4 mg BID*	48	11.84 (7.11, 16.58)	5.63 (1.48, 9.77)	10.31 (5.49, 15.12)	8.34 (4.53, 12.15)
Moxifloxacin 400 mg QD †	45	19.26‡ (15.49, 23.03)	8.90 (4.77, 13.03)	19.10‡ (15.32, 22.89)	9.29 (5.34, 13.24)

*At T_{max} of 1 hr; 95% Confidence Interval.
†At T_{max} of 2 hr; 90% Confidence Interval.
‡The effect on QT interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials of other drugs.

The reason for the difference between machine and manual read of QT interval is unclear. The QT effect of tolterodine immediate release tablets appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day. The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped.

Tolterodine's effect on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QTc interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study.

This study was not designed to make direct statistical comparisons between drugs or dose levels. There has been no association of Torsade de Pointes in the international post-marketing experience with DETROL or DETROL LA [see ***WARNINGS and PRECAUTIONS** (5.6)*].

12.3 Pharmacokinetics

Absorption: In a study with ^{14}C-tolterodine solution in healthy volunteers who received a 5-mg oral dose, at least 77% of the radiolabeled dose was absorbed. C_{max} and area under the concentration-time curve (AUC) determined after dosage of tolterodine immediate release are dose-proportional over the range of 1 to 4 mg. Based on the sum of unbound serum concentrations of tolterodine and 5-HMT ("active moiety"), the AUC of tolterodine extended release 4 mg daily is equivalent to tolterodine immediate release 4 mg (2 mg bid). C_{max} and C_{min} levels of tolterodine extended release are about 75% and 150% of tolterodine immediate release, respectively. Maximum serum concentrations of tolterodine extended release are observed 2 to 6 hours after dose administration.

Effect of Food: There is no effect of food on the pharmacokinetics of tolterodine extended release.

Distribution: Tolterodine is highly bound to plasma proteins, primarily α_1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. 5-HMT is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine and 5-HMT averages 0.6 and 0.8, respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine following administration of a 1.28-mg intravenous dose is 113 ± 26.7 L.

Metabolism: Tolterodine is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active metabolite, 5-HMT. Further metabolism leads to formation of the 5-carboxylic acid and *N*-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3% of the metabolites recovered in the urine, respectively.

Variability in Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6, the enzyme responsible for the formation of 5-HMT from tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to *N*-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers." Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HMT.

Excretion: Following administration of a 5-mg oral dose of ^{14}C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (<2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as 5-HMT. A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine extended release and 5-HMT in extensive (EM) and poor (PM) metabolizers is provided in Table 3. These data were obtained following single and multiple doses of tolterodine extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM).

Table 3 Summary of Mean (±SD) Pharmacokinetic Parameters of Tolterodine Extended Release and its Active Metabolite (5-Hydroxymethyl Tolterodine) in Healthy Volunteers

	Tolterodine				5-Hydroxymethyl Tolterodine			
	t_{max}* (h)	C_{max} (µg/L)	C_{avg} (µg/L)	$t_{½}$ (h)	t_{max}* (h)	C_{max} (µg/L)	C_{avg} (µg/L)	$t_{½}$ (h)
Single dose 4 mg†								
EM	4(2–6)	1.3(0.8)	0.8(0.57)	8.4(3.2)	4(3–6)	1.6(0.5)	1.0(0.32)	8.8(5.9)
Multiple dose 4 mg								
EM	4(2–6)	3.4(4.9)	1.7(2.8)	6.9(3.5)	4(2–6)	2.7(0.90)	1.4(0.6)	9.9(4.0)
PM	4(3–6)	19(16)	13(11)	18(16)	—‡	—	—	—

C_{max} = Maximum serum concentration; t_{max} = Time of occurrence of C_{max};
C_{avg} = Average serum concentration; $t_{1/2}$ = Terminal elimination half-life.
*Data presented as median (range).
†Parameter dose-normalized from 8 to 4 mg for the single-dose data.
‡ = not applicable.

Drug Interactions:

Potent CYP2D6 Inhibitors: Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate release in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in C_{max} and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT, the pharmacologically active metabolite of tolterodine). Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be CYP2D6 extensive metabolizers of tolterodine immediate release to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate release and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered.

Potent CYP3A4 inhibitors: The effect of a 200-mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were CYP2D6 poor metabolizers. In the presence of ketoconazole, the mean C_{max} and AUC of tolterodine increased by 2- and 2.5-fold, respectively. Based on these findings, other potent CYP3A4 inhibitors may also lead to increases of tolterodine plasma concentrations.

For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, miconazole, clarithromycin, ritonavir, the recommended dose of DETROL LA is 2 mg daily [*see **DOSAGE AND ADMINISTRATION(2.3)***].

Warfarin: In healthy volunteers, coadministration of tolterodine immediate release 4 mg (2 mg bid) for 7 days and a single dose of warfarin 25 mg on day 4 had no effect on prothrombin time, Factor VII suppression, or on the pharmacokinetics of warfarin.

Oral Contraceptives: Tolterodine immediate release 4 mg (2 mg bid) had no effect on the pharmacokinetics of an oral contraceptive (ethinyl estradiol 30 µg/levo-norgestrel 150 µg) as evidenced by the monitoring of ethinyl estradiol and levo-norgestrel over a 2-month period in healthy female volunteers.

Diuretics: Coadministration of tolterodine immediate release up to 8 mg (4 mg bid) for up to 12 weeks with diuretic agents, such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide, or furosemide, did not cause any adverse electrocardiographic (ECG) effects.

Effect of tolterodine on other drugs metabolized by Cytochrome P450 enzymes: Tolterodine immediate release does not cause clinically significant interactions with other drugs metabolized by the major drug-metabolizing CYP enzymes. *In vivo* drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole. *In vitro* data show that tolterodine immediate release is a competitive inhibitor of CYP2D6 at high concentrations (K_i 1.05 µM), while tolterodine immediate release as well as the 5-HMT are devoid of any significant inhibitory potential regarding the other isoenzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), exposure margins were approximately 6-9 times, 7 times, and 11 times the clinical exposure to the pharmacologically active components of DETROL® LA (based on AUC of tolterodine and its 5-HMT metabolite). At these exposure margins, no increase in tumors was found in either mice or rats.

No mutagenic or genotoxic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in 4 strains of *Salmonella typhimurium* and in 2 strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative *in vivo* in the bone marrow micronucleus test in the mouse.

In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (about 9-12 times the clinical exposure via AUC), neither effects on reproductive performance or fertility were seen. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

14 CLINICAL STUDIES

DETROL LA Capsules 2 mg were evaluated in 29 patients in a Phase 2 dose-effect study. DETROL LA 4 mg was evaluated for the treatment of overactive bladder with symptoms of urge urinary incontinence and frequency in a randomized, placebo-controlled, multicenter, double-blind, Phase 3, 12-week study. A total of 507 patients received DETROL LA 4 mg once daily in the morning and 508 received placebo. The majority of patients were Caucasian (95%) and female (81%), with a mean age of 61 years (range, 20 to 93 years). In the study, 642 patients (42%) were 65 to 93 years of age. The study included patients known to be responsive to tolterodine immediate release and other anticholinergic medications, however, 47% of patients never received prior pharmacotherapy for overactive bladder. At study entry, 97% of patients had at least 5 urge incontinence episodes per week and 91% of patients had 8 or more micturitions per day.

The primary efficacy assessment was change in mean number of incontinence episodes per week at week 12 from baseline. Secondary efficacy measures included change in mean number of micturitions per day and mean volume voided per micturition at week 12 from baseline.

Patients treated with DETROL LA experienced a statistically significant decrease in number of urinary incontinence per week from baseline to last assessment (week 12) compared with placebo as well as a decrease in the average daily urinary frequency and an increase in the average urine volume per void.

Mean change from baseline in weekly incontinence episodes, urinary frequency, and volume voided between placebo and DETROL LA are summarized in Table 4.

Table 4. 95% Confidence Intervals (CI) for the Difference between DETROL LA (4 mg daily) and Placebo for Mean Change at Week 12 from Baseline*

	DETROL LA (n=507)	Placebo (n=508) †	Treatment Difference, vs. Placebo (95% CI)
Number of incontinence episodes/ week Mean Baseline Mean Change from Baseline	22.1 –11.8 (SD 17.8)	23.3 –6.9 (SD 15.4)	-4.8 ‡ (–6.9, –2.8)
Number of micturitions/day Mean Baseline Mean Change from Baseline	10.9 –1.8 (SD 3.4)	11.3 –1.2 (SD 2.9)	-0.6 ‡ (–1.0, –0.2)
Volume voided per micturition (mL) Mean Baseline Mean Change from Baseline	141 34 (SD 51)	136 14 (SD 41)	20 ‡ (14, 26)

SD = Standard Deviation.
* Intent-to-treat analysis.
† 1 to 2 patients missing in placebo group for each efficacy parameter.
‡ The difference between DETROL LA and placebo was statistically significant.

16 HOW SUPPLIED/STORAGE AND HANDLING

DETROL LA Capsules are supplied as follows:

Bottles of 30		Bottles of 500	
2 mg Capsules	NDC 0009-5190-01	2 mg Capsules	NDC 0009-5190-03
4 mg Capsules	NDC 0009-5191-01	4 mg Capsules	NDC 0009-5191-03
Bottles of 90		Unit Dose Blisters	
2 mg Capsules	NDC 0009-5190-02	2 mg Capsules	NDC 0009-5190-04
4 mg Capsules	NDC 0009-5191-02	4 mg Capsules	NDC 0009-5191-04

Store at 20°–25°C (68°–77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling (17.2)*.

17.1 Information for Patients

Patients should be informed that antimuscarinic agents such as DETROL LA may produce the following effects: blurred vision, dizziness, or drowsiness. Patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined.

17.2 FDA Approved Patient Labeling

Rx only

Distributed by
Pfizer
Pharmacia & Upjohn Company
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PATIENT INFORMATION

DETROL® LA (DE-trol el-ay)
(tolterodine tartrate extended release capsules)

Read the Patient Information that comes with DETROL LA before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or your treatment. Only your doctor can determine if treatment with DETROL LA is right for you.

What is DETROL LA?

DETROL LA is a prescription medicine for **adults** used to treat the following symptoms due to a condition called **overactive bladder**:

- having a strong need to urinate with leaking or wetting accidents (urge urinary incontinence)
- having a strong need to urinate right away (urgency)
- having to urinate often (frequency)

DETROL LA did not help the symptoms of overactive bladder when studied in children.

What is overactive bladder?

Overactive bladder happens when you cannot control your bladder muscle. When the muscle contracts too often or cannot be controlled, you get symptoms of overactive bladder, which are leakage of urine (urge urinary incontinence), needing to urinate right away (urgency), and needing to urinate often (frequency).

Who should not take DETROL LA?

Do not take DETROL LA if:

- you have trouble emptying your bladder (also called "urinary retention")
- your stomach empties slowly (also called "gastric retention")
- you have an eye problem called "uncontrolled narrow-angle glaucoma"
- you are allergic to DETROL LA or to any of its ingredients. See the end of this leaflet for a complete list of ingredients

What should I tell my doctor before starting DETROL LA?

Before starting DETROL LA, tell your doctor about all of your medical conditions, including if you:

- have any stomach or intestinal problems
- have trouble emptying your bladder or you have a weak urine stream
- have an eye problem called narrow-angle glaucoma
- have liver problems
- have kidney problems
- have a condition called myasthenia gravis
- or any family members have a rare heart condition called QT prolongation (long QT syndrome)
- are pregnant or trying to become pregnant. It is not known if DETROL LA could harm your unborn baby
- are breastfeeding. It is not known if DETROL LA passes into your milk and if it can harm your child

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Other drugs can affect how your body handles DETROL LA. Your doctor may use a lower dose of DETROL LA if you are taking:

- Certain medicines for fungus or yeast infections such as Nizoral® (ketoconazole), Sporanox® (itraconazole), or Monistat® (miconazole)
- Certain medicines for bacteria infections such as Biaxin® (clarithromycin)
- Certain medicines for treatment of HIV infection such as Norvir® (ritonavir), Invirase® (saquinavir), Reyataz® (atazanavir)
- Sandimmune® (cyclosporine) or Velban® (vinblastine)

Know the medicines you take. Keep a list of them with you to show your doctor or pharmacist each time you get a new medicine.

How should I take DETROL LA?

- Take DETROL LA exactly as prescribed. Your doctor will prescribe the dose that is right for you. Do not change your dose unless told to do so by your doctor.
- Take DETROL LA capsules once a day with liquid. Swallow the whole capsule. Tell your doctor if you cannot swallow a capsule.
- DETROL LA can be taken with or without food.
- Take DETROL LA the same time each day.
- If you miss a dose of DETROL LA, begin taking DETROL LA again the next day. Do not take 2 doses of DETROL LA in the same day.
- If you took more than your prescribed dose of DETROL LA, call your doctor, or poison control center, or go to the hospital emergency room.

What are possible side effects of DETROL LA?

The most common side effects with DETROL LA are:

- dry mouth
- constipation
- headache
- stomach pain

Medicines like DETROL LA can cause blurred vision, dizziness, or drowsiness.

Use caution while driving or doing other dangerous activities until you know how DETROL LA affects you.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

These are not all the side effects with DETROL LA. For a complete list, ask your doctor or pharmacist.

How do I store DETROL LA?

- Store DETROL LA at room temperature, 68° - 77°F (20° - 25°C); brief periods permitted between 59° - 86°F (15° - 30°C). Protect from light. Keep in a dry place.
- **Keep DETROL LA and all medicines out of the reach of children.**

General Information about DETROL LA

Medicines are sometimes prescribed for conditions that are not in the patient information leaflet. Only use DETROL LA the way your doctor tells you. Do not share it with other people even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about DETROL LA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DETROL LA that is written for health professionals. You can also visit www.DETROLLA.com on the Internet, or call 1-888-4-DETROL (1-888-433-8765).

What are the ingredients in DETROL LA?

Active ingredients: tolterodine tartrate

Inactive ingredients: sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C Blue #2. 2 mg capsule also contains yellow iron oxide. Capsules have pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

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